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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,749	11/29/2001	Gerritdina Hendrika Van Geel-Schutten	BO43388-CIP	3543

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,749	VAN GEEL-SCHUTTEN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 6-25* is/are pending in the application.

4a) Of the above claim(s) *14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-13,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1, 3, 6-25 are still at issue and are present for examination. Claims 1, 3, 6-13, 24 and 25 are now under consideration. Claims 14-23 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 2-11-03, paper No.12, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 3, 6-13 which depend from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1recites the phrase "60% amino acid activity" in line 3. It is not clear to the Examiner as to whether applicants are claiming an isolated protein that exhibits 60% activity of SEQ ID NO:2 or an isolated protein that exhibits 60% amino acid identity with SEQ ID NO:2, thus rendering the claim indefinite. It appears that applicants intended to recite "60% amino acid identity". If this is so amending the claim accordingly would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6-13, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a glycosyltransferase enzyme with SEQ ID NO:2 isolated from L.reuteri, does not reasonably provide enablement for any glycosyltransferase comprising fragments of SEQ ID NO:2 (such as 100 or 200 amino acids) that are 50%, 55%, 60%, 65% or 70% identical to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 3, 6-13, 24 and 25 are so broad as to encompass any glycosyltransferase from any source that comprises fragments of SEQ ID NO:2 (such as 100 or 200 amino acids) that are 50%, 55%, 60%, 65% or 70% identical to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glucosyl transferases broadly encompassed by the

claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a single glycosyltransferase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any glycosyltransferase comprising fragments of SEQ ID NO:2 (such as 100 or 200 amino acids) that are 50%, 55%, 60%, 65% or 70% identical to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants because the specification does not establish: (A) regions of the protein structure which may be modified without effecting its activity; (B) the general tolerance of glucosyl transferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues in any glycosyltransferase or its

specific fragments with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including glucosyl transferases with an enormous number of amino acid modifications of the glycosyltransferase of SEQ ID NOS: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of glucosyl transferases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing that they have amended the claims to recite a practically full length protein having at least 60% identity with a specified sequence exhibiting glycosyltransferase activity. Applicants argue that the specification provides the general methods for making and using the claimed proteins. Applicants argue that while claims 7-8 are directed towards the catalytic domain, claims 9 to 10 are directed towards the glucan binding domain and therefore, the claimed invention is supported by an enabling disclosure. Examiner respectfully disagrees with such an argument as being persuasive to overcome the rejection because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants requires that one

of ordinary skill in the art, to know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property (i.e., both structure and function). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, (i.e., polypeptides which are 50%, 55%, 60%, 65% or 70% identical to either full length SEQ ID NO:2 or parts of the same) the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue on the polypeptide or specific parts of the polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6-12, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by van Geel-Schutten et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703). This rejection is based upon the public availability of a printed publication. Claims 1, 3, 6-12, 24 and 25 of the instant application are drawn to an isolated protein having glycosyltransferase activity and whose amino acid sequence is 50-70% identical to SEQ ID NO:2, or fragments of the same wherein amino acid at specific position corresponding to their position on SEQ ID NO:2 are changed and which can produce a glucan having 38-48% 4-linked anhydroglucose units, 17-28% 6-linked anhydroglucose units and 7-20% 4,6-linked anhydroglucose units. van Geel-Schutten (b) et al. disclose a glycosyltransferase also known as glucansucrase isolated from *L.reuteri*. Since the enzyme is isolated from the same microorganism that is claimed by the applicants, Examiner takes the position that the enzyme disclosed in the reference and the enzyme disclosed in the instant application are the same even though the reference does not disclose the amino acid sequence. Examiner also takes the position that amino acid sequence information is inherent to the proteins/enzymes and therefore the enzyme in the reference has the same sequence information as that disclosed by the applicants. Thus van Geel-Schutten (c) et al. anticipate claims 1, 3, 6-12, 24 and 25 of this application as written.

In response to the previous Office action, applicants have traversed the above rejection arguing that the above reference fails to disclose or suggest specific enzyme and that the article vaguely refers to the role of biosynthetic enzymes and thus, "it cannot be said that a protein (enzymatic or not) was isolated or characterized" and submit that the reference does not disclose or suggest the claimed invention. Examiner respectfully disagrees with such an argument and asserts that such an argument is not persuasive to overcome the above rejection. The reference clearly identifies

the strains of Lactobacillus that produce large amounts of exopolysaccharide. In addition, the reference also discloses the "enzyme localization studies" on page 698, in which the preparation of the enzyme composition is taught. The reference clearly discloses EPS biosynthetic enzyme activity obtained from Lactobacillus strains. Therefore contrary to applicants arguments, the above reference clearly anticipates the claimed invention.

Examiner has withdrawn the rejection of the above claims 1, 3, 6-12, 24 and 25 as being anticipated by van Geel-Schutten et al. (a)(Med. Fac. Landbouww, Gent Univ., 2000, Vol. 65/3a :197-201) as applicants have claimed priority to parent application. Examiner has withsddrawn the rejection of above claims as being anticipated by van Geel-Schutten et al. (Appl Environ Microbiol, Vol. 65(7):3008-14, 1999) in view of the declaration filed under 37 CFR 1.132 by the inventors.

In view of the claim amendments made by the applicant, Examiner has withdrawn the rejection of claims 1, 4, 12 and 13 under 35 U.S.C. 102(b) as being anticipated by Giffard et al. (WO 96/06173-A1, 2-29-1996).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over van Geel-Schutten et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703) as applied to claims 1, 3, 6-12, 24 and 25 above, and further in view of the methods taught by Ausubel et al. (Short Protocols in Molecular Biology, 1997) regarding protein purification, sequencing and molecular cloning. The reference of van Geel-Schutten as applied to claims 1, 3, 6-12, 24 and 25, drawn to an isolated and purified glycosyltransferase isolated from *L.reuteri* has been discussed above.

With the enzyme preparations provided by van Geel-Schutten et al. it would have been obvious to one of ordinary skill in the art to make a recombinant enzyme of the same by further purifying the enzyme, microsequencing said purified protein, designing a probe based on the microsequencing data and analyzing a cDNA library of the lactic acid bacteria leading to the isolation of a cDNA clone and expressing such a clone to obtain a recombinant protein using the methods taught by Ausubel et al. Examiner would like to point out here that molecular cloning has indeed become common knowledge in the art. There are innumerable books and manuals that teach said techniques. Commercial cloning kits specifically made for screening and isolating clones from bacterial, plant or animal sources are also available. One of ordinary skill in the art would be motivated to do so in order to make the enzyme in large quantities in view of its use for making glucans, which have great demand in the food industry. One of ordinary skill in the art would have a reasonable expectation of success since van Geel-Schutten et al. (a, b) teach enzyme preparation and the art or Ausubel et al. teach the methods for making recombinant proteins.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that van Geel-Schutten references fail to qualify as prior arts. Applicants argue that the reference of van Geel-Schutten (b) et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703) specifically does not disclose or suggest any information on the functionality or structure of the claimed proteins and thus one of ordinary skill in the art would not be able to deduce whether a single enzyme or a complex of enzymes would be responsible for producing the polysaccharide. Examiner respectfully disagrees with the applicants. This is because both the above references are prior art documents and both references clearly teach enzyme preparations responsible for exopolysaccharide synthesis. While the references may not teach a recombinant enzyme preparation and amino acid sequences of said enzyme, as explained above, it would have been quite obvious to those skilled in the art to arrive at such inventions.

Applicants also argue that it was inappropriate for the Examiner to argue on the basis of "common knowledge". Even though molecular cloning techniques are well established and well known in the art and what is well known in the art need not be taught again, without acquiescing to applicant's arguments, Examiner has now included a reference to support his rejection. Therefore, contrary to applicants' arguments, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
April 29, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1300~~ 1600